

Comment

GS is President of the Association des Correspondants Auprès des Nations Unies.

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Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate

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Many trials in breast cancer have investigated various aspects of locoregional and systemic treatments. Combination of the results of these trials in a meticulous meta-analysis, as has been done several times by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), fills the gaps in evidence and knowledge by conclusively showing significant trends and differences.

Following publication of the effect of radiotherapy after breast-conserving therapy,¹ the EBCTCG now presents results for postmastectomy radiotherapy in *The Lancet*.² The central issue is the role of postmastectomy radiotherapy in patients with one to

three involved axillary lymph nodes, which is currently a matter of debate in many countries.³ Whereas the earlier results were essentially confirmed in this report,^{1,4} we get more insight into the effect of the extent of lymph-node involvement, the number of examined axillary lymph nodes, and the use of adjuvant systemic therapy. Overall, postmastectomy radiotherapy improves locoregional disease-free survival, overall disease-free survival, and breast-cancer-specific survival for all patients with involvement of axillary lymph nodes, irrespective of the number of involved lymph nodes and of administration of adjuvant systemic therapy. This improvement is not only statistically significant, but also clinically relevant.

The proportional reductions in rates of recurrence and mortality were independent of the administration of systemic therapy. Whether this finding also applies to patients treated with more contemporary regimens remains to be seen. We need to continue evaluating results of the contemporary multidisciplinary approach in breast cancer to better understand the complex interaction between respective contributions of systemic and locoregional treatments to the final outcome, including survival and toxic effects. As Punglia and colleagues⁵ pointed out, the contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment. Punglia and colleagues' bell-shaped curve,⁵ however, misses the component of metastatic risk of the primary tumour. Combining both, the influence of both the effectiveness of systemic therapy and metastatic risk of the primary tumour can be used to estimate the

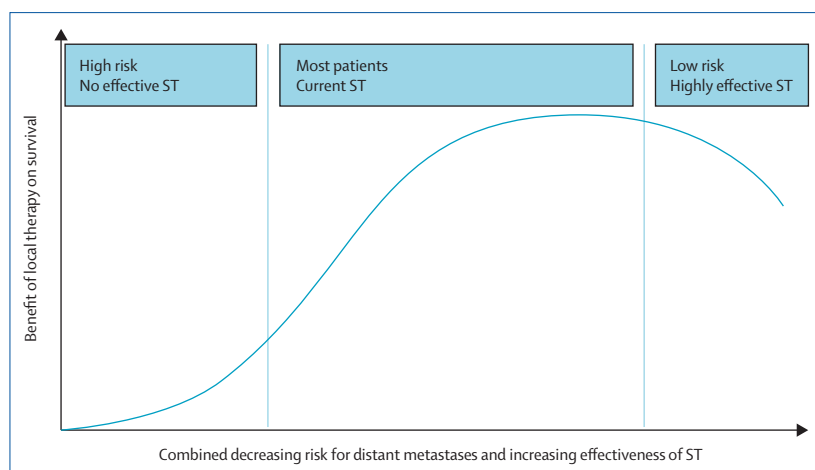


Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour. Patients in the left part of the slope have high-risk disease without effective systemic therapy and are not expected to benefit from improving locoregional treatments. For patients in the right part of the slope, treatment deintensification (surgery, radiation, or systemic therapy) might be appropriate. The middle group will represent most past and current patients with breast cancer, for whom an optimum multidisciplinary approach results in the greatest benefit.

contribution of improved locoregional treatment to the final outcome (figure). For many patients, improvement of systemic therapy will decrease the risk of death due to distant metastasis, after which the importance of optimised locoregional control—which will already be better after systemic treatment—will, relatively, contribute more to survival.

As the EBCTCG outlines,² interpretation of the findings should take into account the decreased locoregional recurrence rates during recent decades owing to improvements in diagnostic and therapeutic procedures. However, the complex interaction between locoregional and distant recurrences as a first event (illustrated in the appendix of the Article) clearly shows that the two types of event should not be considered individually as separate events but taken together. Improvements in locoregional treatments will only directly affect the development and further spread of subclinical locoregional tumour deposits. Moreover, we should realise that the incidence of locoregional recurrences at diagnosis of distant metastasis is underestimated because of a lack of relevance of its detection and no routine accurate diagnosis, especially for regional recurrences, making the latter a poor endpoint for trials evaluating locoregional treatments.⁶ Also of note in this respect is the finding that the one in four rule from earlier EBCTCG meta-analyses (ie, for every four recurrences avoided about one life was saved) cannot be generalised to all patient groups; in the present analysis, about one breast cancer death at 20 years was avoided for every 1.5 recurrences avoided at 10 years.^{1,2,4}

This meta-analysis also shows the importance of the extent of axillary surgery, with a greater benefit of postmastectomy radiotherapy for patients who had axillary sampling as compared with a complete axillary dissection, even in node-negative patients. However, it should be noted that the sentinel lymph-node procedure was not yet used in these trials, so care should be taken not to extrapolate the results to this now common procedure. Notwithstanding this limitation, the findings warn against the current trend of omission of further regional treatment after a positive sentinel lymph node on the basis of data for regional recurrences and short-term follow-up.⁷

As reported before, radiotherapy can increase the rate of deaths not related to breast cancer, mainly by inducing cardiac diseases and secondary cancers.^{8–10} This

outcome lowers the benefit of radiotherapy on breast cancer mortality after longer follow-up, as shown in the appendix of the Article. However, modern radiotherapy techniques allow the non-intended dose to organs at risk to be decreased, while at the same time improving coverage of the target volumes.^{11,12} Therefore, continued follow-up is needed to understand fully the ultimate influence of radiotherapy on breast-cancer-related mortality and on late toxic effects.

The results of this EBCTCG meta-analysis clearly confirm that postmastectomy radiotherapy should be considered equally for patients with one to three involved axillary lymph nodes as it should be for patients with four or more affected axillary lymph nodes. The same considerations concerning regional radiotherapy also seem to be valid for patients treated with breast-conserving therapy.^{1,2} Here, the addition of regional radiotherapy to whole breast irradiation adds less to the burden of treatment to the patient, on the condition that long-term toxic effects can be avoided with modern radiotherapy techniques.

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I declare that I have no competing interests.

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116E rotavirus vaccine development: a successful alliance

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In *The Lancet*, Nita Bhandari and colleagues' study¹ about the efficacy of the new 116E rotavirus vaccine in Indian infants offers an opportunity to address the substantial lag in translation of scientific progress for the benefit of the world's most vulnerable population. Vaccination is considered to be second only to access to potable water in its potential cost-effectiveness as a health-care strategy for improving child health. Most childhood deaths from vaccine-preventable diseases, such as *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and rotavirus, happen in low-income countries.² However, introduction of life-saving vaccines, such as Hib conjugate vaccine, into national immunisation programmes in low-income countries has lagged by as much as 20 years behind implementation in high-income settings.³ Of the many factors responsible, constraints around vaccine affordability and supply are key.

In the past decade, progress has been made in reducing the delay in the introduction of new childhood vaccines (eg, those against pneumococcus and rotavirus) into immunisation programmes between

developed and developing countries. This progress is largely attributable to international donor funding coordinated under the auspices of the GAVI Alliance, which among other things provides cofinancing for vaccine procurement at discounted prices negotiated with manufacturers for countries that meet an income threshold for eligibility (presently a gross national income per person of \leq US\$1550). However, the sustainability of the GAVI process, in which countries are expected to take over ownership of funding for vaccine procurement once their gross national income per person exceeds GAVI's eligibility threshold, remains a concern. One way to address this challenge is to explore approaches to development of low-cost, safe, and effective vaccines that are affordable for low-income countries.

Within this framework, the development of 116E rotavirus vaccine provides a model of a successful tripartite alliance between donors, governmental institutions, and a willing private sector, to ensure that vaccines are developed at affordable prices. Clinical development of the 116E vaccine was undertaken by an emerging Indian vaccine manufacturer—Bharat Biotech—with full partnership and partial financial support from the Department of Biotechnology of the Indian Government, and with technical and financial support from a consortium of international partners and donors. In lieu of public sector support to offset some of the research and development costs, the manufacturer has committed to making the vaccine available to the public sector at less than \$1 per dose for a three-dose series. This regime is in comparison to the discounted cost, \$2.50 per dose for a two-dose series and \$3.50 per dose for a three-dose series, of two other licensed rotavirus vaccines that GAVI pays for countries that procure vaccine through UNICEF.⁴ Beneficiary low-income countries contribute \$0.40 in co-financing for a full series of either vaccine.⁵



Narinder Nanu/AFP/Getty Images